Remarks/Arguments

Claims 2-10 are pending in the above-identified application. Claims 1 and 11 were previously withdrawn. The citations to the specification included throughout this response are to the paragraph numbers of the published application (US 2006/0052424).

Objection to Specification; Rejection Of Claim 2 Under 35 U.S.C. § 112, Second Paragraph

The Office Action objects to the phrase "or deleted" with regard to substituent R^3 in paragraph 7 of the specification for allegedly being unclear, and rejects the identical language in claim 2 under 35 U.S.C. § 112, second paragraph, as indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. Applicants respectfully disagree.

Paragraph 7 and claim 2 describe the substituent A^1 as follows:

> A^1 is H, the side chain of any naturally occurring α-amino acid, or is of the following formula,
>
> $$-(CH_2)_m-Y-(CH_2)_n-R^3X^3$$
>
> wherein ... R^3 is straight chain or branched C_{1-8} alkylidene, straight chain or branched C_{1-8} alkylene, C_{3-10} cycloalkylidene, C_{3-10} cycloalkylene, phenylene, C_{6-14} arylalkylidene, C_{6-14} arylalkylene, ***or deleted*** ...

(¶ 7; claim 2 at 48) (emphasis added). One of skill in the art would understand that the phrase "or deleted" means that the substituent R^3 may optionally be excluded or deleted from the formula, resulting in the formula $-(CH_2)_m-Y-(CH_2)_n-X^3$. This language has been allowed in related applications without objections. In related U.S. Patent No. 6,838,447[1], to which this application claims priority, the specification and claim 1 recite:

> A^1 is H, the side chain of any naturally occurring α-amino acid, or is of the following formula,

[1] See also U.S. Patent Nos. 6,335,358 and 6,458,825.

$$-(CH_2)_m-Y-(CH_2)_n-R^3X^3$$

> wherein ... R^3 is straight chain or branched C_{1-8} alkylidene, straight chain or branched C_{1-8} alkylene, C_{3-10} cycloalkylidene, C_{3-10} cycloalkylene, phenylene, C_{6-14} arylalkylidene, C_{6-14} arylalkylene, ***or deleted*** ...

(col. 3, lines 2 to 19; col. 93, line 57 to col. 94, line 35) (emphasis added).

The presence of the limitation "or deleted" for the substituent R^3 in the '447 patent suggests the limitation "or deleted" is not indefinite to one of skill in the art. Accordingly, Applicants respectfully submit that the present objection and rejection should both be reconsidered and withdrawn.

Rejection Of Claims 2-10 Under 35 U.S.C. § 112, First Paragraph

Claims 2-10 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to provide an enabling disclosure. The Office Action asserts that the specification does not enable one skilled in the art to use the disclosed invention to treat all types of cancer. Claims 2 and 5-10 also stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to provide an enabling disclosure. The Office Action asserts that the specification does not enable one skilled in the art to use any compound of the formula listed in claim 2 other than lactacystin. Applicants respectfully traverse.

> Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation .... The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

In re Wands, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988) (citations omitted). However, the Office Action asserts that that the specification does not enable one skilled in the art to use the disclosed invention without engaging in undue experimentation, citing *Wands*.

The Office Action asserts that claims 2-4 are broad because "they are drawn to a method of treating various types of cancer" (Office Action at 3). Applicants respectfully disagree.

> To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts.

In re Goffe, 191 U.S.P.Q. 429, 431 (C.C.P.A. 1976). Claims 2-4 are directed towards methods of treating cancer by administering the compounds disclosed in claim 2. No other compounds are claimed. No methods of treating or preventing other conditions or disease states are claimed. The specification discloses four compounds with biological activity against osteosarcoma cells in vitro (see Table 3 at pages 38-39). Applicants are not required to submit data for every compound of claim 2, or for every cancer cell type of claims 3 and 4. Demanding data beyond what Applicants have found will work "would not serve the constitutional purpose of promoting progress in the useful arts," *id.*, and is not necessary to fulfill the enablement requirement of § 112 as set forth in *Wands*.

The Office Action states that the specification does not provide guidance for treating various types of cancer using a compound of the formula listed in claim 2. Applicants respectfully disagree. Claims 2-10 are directed towards a method of treating cancer with lactacystin analogs. The specification teaches that the compounds disclosed in claims 2-10 inhibit the proteasome. For example, paragraph 148 states:

> [T]he disclosed compounds are also useful as diagnostic agents (e.g., in diagnostic kits or for use in clinical laboratories) for screening for proteins (e.g., enzymes, transcription factors) processed by the proteasome. The disclosed compounds are also

> useful as research reagents for specifically binding the X/MB1 subunit or α-chain [of the proteasome] and ***inhibiting the proteolytic activities*** associated with it. For example, the activity of (and specific inhibitors of) other subunits of the proteasome can be determined.

(emphasis added). Paragraph 26 teaches "[t]he compounds disclosed herein are highly selective for the proteasome, and do not inhibit other proteases such as trypsin, a-chymotrypsin, calpain I, calpain II, papain, and cathepsin B."

The specification also teaches that proteasome inhibitors may be used to treat or inhibit cancer. For example, paragraph 129 states "[p]roteasome inhibitors are useful for treating conditions such as cancer." Paragraph 143 states "[c]yclins are proteins involved in cell cycle control. The proteasome participates in the degradation of cyclins .... Inhibition of the proteasome inhibits cyclin degradation, and therefore inhibits cell proliferation (e.g., cyclin-related cancers)."

The specification teaches that the compounds disclosed in claims 2-10 are useful for treating cancer. Paragraph 129 states "[e]mbodiments of the invention therefore encompass methods for ... reducing the rate of degradation of p53 protein in a cell, and inhibiting the growth of p53-related cancers." Paragraph 143 explains "[o]ne embodiment of the invention is a method for treating a proliferative disease in a subject (e.g., cancer, psoriasis, or restenosis), including administering to the subject an effective amount of a compound of a formula disclosed herein." "Additional embodiments [of the invention] are methods for affecting the proteasome-dependent regulation of oncoproteins and methods of treating or inhibiting cancer growth ..." (¶ 144). These teachings can also be found elsewhere in the specification (*see, e.g.*, ¶¶ 25, 145, and 151).

Finally, the specification teaches methods of treating cancer in a subject by "administering to the subject an effective amount of a compound disclosed herein" (¶ 143), and "methods of treating or inhibiting cancer growth ... [by] exposing a cell (in vivo, e.g., in a subject or in vitro) to a compound of a formula disclosed herein" (¶ 144). Methods for formulating the claimed compounds are also disclosed (¶¶ 152-156). These methods describe

various routes of administration (¶ 154) and dose ranges (¶ 155). The specification also provides examples detailing in vitro methods for determining biological activity of the disclosed compounds (¶¶ 166-167, 179), and results generated from these methods showing the inhibition of cancer cell cycle progression (Table 3). Therefore, the specification provides sufficient guidance for one of skill in the art to make and use the claimed invention.

The Office Action asserts that the claimed invention is not enabled because Applicants have "not provide[d] any examples for treating various types of cancer" (Office Action at 4). Applicants respectfully disagree. As an initial matter, "[t]he specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation." MPEP § 2164.02 at 2100-189 (citing *In re Borkowski*, 164 U.S.P.Q 642, 645 (C.C.P.A. 1970)). Additionally, "[a]n applicant need not have actually reduced the invention to practice prior to filing." MPEP § 2164.02 at 2100-189. "'The mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it.'" *Gould v. Quigg*, 3 U.S.P.Q.2d 1302, 1304 (Fed. Cir. 1987) (quoting *In re Chilowsky*, 108 U.S.P.Q. 321, 325 (C.C.P.A. 1956)).

The specification discloses methods for testing the disclosed compounds for biological activity against MG-63 osteosarcoma cells and Neuro 2A neuroblastoma cells (¶¶ 166-167, 179). Biologically active compounds inhibit cell cycle progression in MG-63 cells and induce neural outgrowth in Neuro 2A cells (¶ 167). Results are presented in Table 3, which shows biological activity for four different compounds, two of which were tested at multiple concentrations (pages 38-39). Therefore, the specification provides working examples of methods by which one skilled in the art can test the disclosed compounds against cancer cell lines for biological activity.

The Office Action asserts that "it would require undue, unpredictable experimentation to practice the claimed invention" because "one of skill in the art would have to first envision formulation, dosage, duration, route and ... an appropriate animal model system to test the ... compound of formula listed in claim 2" (Office Action at 5). Applicants respectfully disagree.

As an initial matter, exact dosage and formulation data are not required for examination and grant of applications by the PTO:

> [I]t is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation. If one skilled in the art, based on knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate dosage or method of use without undue experimentation, this would be sufficient to satisfy 35 U.S.C. 112, first paragraph.

MPEP § 2164.01(c) at 2100-188. Furthermore, the MPEP states:

> The Office must confine its review of patent applications to the statutory requirements of the patent law. Other agencies of the government have been assigned the responsibility of ensuring conformance to standards established by statute for the advertisement, use, sale or distribution of drugs. The FDA pursues a two-prong test to provide approval for testing. Under that test, a sponsor must show that the investigation does not pose an unreasonable and significant risk of illness or injury and that there is an acceptable rationale for the study.

MPEP § 2107.03 at 2100-36. "FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws." *In re Brana*, 34 U.S.P.Q.2d 1436, 1442 (Fed. Cir. 1995). Exact dose and formulation data are thus required by the FDA before a drug can be used in clinical trials or sold to consumers. Such data are not, however, required by or appropriate for PTO review.

As admitted in the Office Action, the "skill of those in the medical treatment art is high, requiring advanced education and training" (Office Action at 4). Conducting studies to determine a "formulation, dosage, duration, route, and, in the case of human treatment, an appropriate animal model system" (Office Action at 5) is well within the skill of those of the art,

and thus is not undue experimentation. Furthermore, time consuming, difficult, and expensive tests do not constitute undue experimentation if they are routine for those of skill in the art. *See, e.g.*, MPEP § 2164.06 at 2100-194 ("In the chemical arts, ... [t]ime and difficulty of experiments are not determinative if they are merely routine"); *United States v. Telectronics, Inc.*, 8 U.S.P.Q.2d 1217 (Fed. Cir. 1988) (finding the amount of experimentation not undue where "[t]he only impediments are the time and cost of a dose response study, which the district court found could be performed by 'those who were expert in the field and actually working with bone, doing electrical stimulation experiments ...' i.e., those skilled in the art").

The use of other proteasome inhibitors to treat cachexia associated with cancer is already known to those of skill in the medical treatment art (*see* U.S. Patent No. 5,340,736). Thus those of skill in the art already know the safety, toxicity, dose ranges, and formulations for proteasome inhibitors, or they know how to conduct studies to determine these parameters. Therefore, the claimed invention is enabled without "specific examples of dosages for human use or even animal tests." *In re Bundy*, 209 U.S.P.Q. 48, 51 (C.C.P.A. 1981). *See also Cross v. Iizuka*, 224 U.S.P.Q. 739, 748 (Fed. Cir. 1985) (finding enablement where those skilled in the art knew the dose for an IC_{50} effect for related compounds because this known dose could serve as a starting point for dose determination experiments, even though the specification "fail[ed] to reveal dosages for the novel compounds per se"); MPEP § 2164.01(c) at 2100-188 ("If one skilled in the art, based on knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate dosage or method of use without undue experimentation, this would be sufficient to satisfy 35 U.S.C. 112, first paragraph.").

The specification thus provides sufficient information to allow the skilled artisan to practice the invention. Formulations are disclosed in paragraphs 153-155. Dose ranges, duration, and a route of delivery are disclosed in paragraph 155. Proteasome inhibitors are known to and used by those of skill in the art (*see* U.S. Patent No. 5,340,736). The specification enables the claimed invention because it provides "formulations, dosages, durations, and a route of delivery" (Office Action at 5), and because determining these parameters is routine to those of skill in the art. Accordingly, Applicants respectfully submit that the present § 112 rejection should be reconsidered and withdrawn.

Rejection Of Claims Under 35 U.S.C. § 102(a)

Claims 2-5, 9 and 10 stand rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Fenteany *et al.*, *Proc. Natl. Acad. Sci. USA* **91**:3345-3362 (1994). Applicants respectfully traverse.

Claims 2-5, 9 and 10 are directed towards methods of treating cancer using lactacystin analogues. The Office Action alleges that Fenteany *et al.* teaches that clasto lactacystin β-lactone inhibits cell cycle progression in an osteosarcoma cell line. Fenteany *et al.*, however, does ***not*** teach that clasto lactacystin β-lactone may be used to treat cancer. Unlike the instant application where Applicants realized that lactacystin and lactacystin analogs can inhibit the proteasome and may therefore be used to treat cancer, there is no statement suggesting inhibition of the proteasome, or of cancer treatment, in the cited reference.

The experiments disclosed in Fenteany *et al.* were conducted to determine whether "[l]actacystin may prove to be a useful reagent for studying ***the signal transduction pathways*** involved in neuronal differentiation and the induction of bipolar morphology [in neurons]" (page 3358, column 1, last paragraph). Fenteany *et al.* proposes mechanisms of action for these findings (page 3362, column 1, second full paragraph through first paragraph of column 2), but does not mention proteasome inhibition or cancer treatments.

Fenteany *et al.* concludes by stating:

> The results of these analog studies suggest the possibility that covalent modification of a target molecule may be important in ***mediating the effects of lactacystin***. Defining the direct molecular target of lactacystin and the downstream cellular events that are sensitive to this agent may shed light upon the regulatory pathways involved in neuronal differentiation and the induction of bipolar morphology.

(page 3362, column 2, second full paragraph) (emphasis added). If Fenteany *et al.* suggests anything, it is the development of methods to ***mediate the effects of lactacystin*** and to

understand the ***differentiation of neurons***. Conversely, Applicants claim a method of ***promoting the effects of lactacystin*** to inhibit the proteasome, and of ***treating cancer***. Because Fenteany *et al.* illustrates the desirability of ***mediating*** the effects of lactacystin, it actually teaches away from Applicants' method of ***promoting*** the effects of lactacystin. Therefore, Fenteany *et al.* does not anticipate claims 2-5, 9 and 10.

Accordingly, Applicants respectfully submit that the present § 102(a) rejection should be reconsidered and withdrawn.

In addition, for completeness, Applicants note that the Office Action quotes § 102(b), but applied § 102(a) in this rejection. Applicants would like to point out that the cited reference was dated (and believed to be published) on April 12, 1994, as evidenced by the first page of the journal article. See attached the faxed first page of this journal, showing that volume 91, number 8, of PNAS was dated April 12, 1994. The instant application has a priority date of April 12, 1995, and therefore the journal article is not a § 102(b) reference.

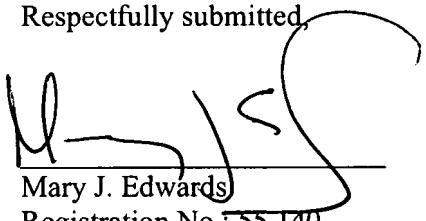
Conclusions

In view of the amendments and arguments set forth above, Applicants submit that each of the rejections contained in the Office Action mailed on December 18, 2006 has been addressed and overcome, and that the claims are in condition for allowance. If the Examiner believes that any further discussion of this communication would be helpful, he is invited to contact the undersigned at the telephone number provided below.

A fee of $1,020 for a three month extension of time is submitted in connection with this response. However, if there are any additional payments due or credits owed, please make them to our Deposit Account No. 08-0219.

Respectfully submitted,

Dated: June 18, 2007



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